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(54) Title: COMPOSITION FOR OPHTHALMIC USE

(57) Abstract

The present invention relates to a composition for the topical administration of bispilocarpic acid diesters to the eye in the form of an aqueous solution, which includes cyclodextrin and optionally a viscosity and enhancing and pH-adjusting agent.

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Composition for ophthalmic use

The present invention relates to a composition for the topical treatment of the eye, which as the active ingredient contains a pilocarpine derivative, specifically a bispilocarpic acid diester. The object of the invention is to eliminate or at least reduce some of the disadvantages associated with the administration of pilocarpine.

Pilocarpine is a drug which is used for the treatment of glaucoma, which drug lowers the ocular pressure by increasing the flow of chamber fluid from the eye. The intraocular pressure reducing effect of pilocarpine is based on the ciliary muscle contracting effect of the drug, by widening the angle of the anterior chamber which is important from the viewpoint of the outflow of the chamber fluid and the outflow of the fluid is facilitated.

Pilocarpine is absorbed into the eye through the cornea. In the cornea it is first absorbed in the dense epithelium layer on the eye surface containing cell membrane lipids (fats) in abundance. However, pilocarpine is not very lipid soluble, wherefore it penetrates relatively little into the corneal epithelium, which delivers pilocarpine through the aqueous stroma and endothelium of the cornea into the fluid of the anterior chamber. From the chamber fluid, pilocarpine has easy access to its action site, the ciliary muscle.

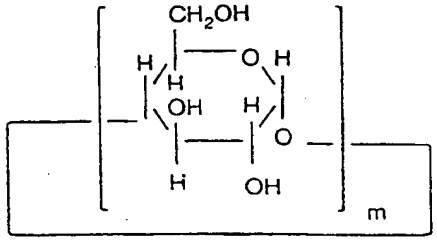
The low absorption into the inner parts of the eye and the short duration of action of pilocarpine administered into the eye, cause difficulties in drug treatment. In order to improve and prolong the action of the drug, pilocarpine must be used in relatively big doses. From this follows that shortly after administration, peak pilocarpine levels are obtained in the chamber fluid, in the iris and the

ciliary muscle which lead to a strong contraction of the pupil (miosis) and accommodation of the eye to seeing at close distance. Pilocarpine, however, leaves the eye rapidly and is therefore administered 3 to 8 times daily, depending on the patient. Each administration is followed by the aforementioned disadvantages.

Efforts have been aimed at solving the disadvantages relating to the poor absorption of pilocarpine, by using pilocarpine prodrugs, i.e. bispilocarpic acid diesters (WO 92/09583). These derivatives are more lipid soluble than pilocarpine and thus provide an improved absorption. They degrade through enzymatic and chemical hydrolysis in the corneal epithelium to liberate the pharmaceutically effective pilocarpine and the ineffective pro-moiety. As the pro-moiety is superfluous in view of the pharmaceutical effect, it is important that the eye is subjected to as small amounts of pro-moiety as possible. Thus it is of importance also for this reason to lower the amount of drug administered to the eye.

The bispilocarpic acid diesters (BD), being very lipid soluble compounds, readily enter the fatty film of the corneal epithelium, wherefore it is of importance to be able to control the rate of absorption of drug into the corneal epithelium and to avoid peak concentrations, which cause i.a. eye irritation.

Cyclodextrins are cyclic oligosaccharides having the general formula



m=6 α-CD
m=7 β-CD
m=8 γ-CD

In the said compounds, the free hydroxy group(s) may be etherified, for example with alkyl or hydroxyalkyl groups, or esterified. Also branched or polymeric cyclodextrins may come into question.

The cyclodextrins are known to form adducts and inclusion complexes with a number of compounds and it is also known to administer drugs complexed with cyclodextrins in order to improve for example the solubility and the stability of the drug. Increased solubility and stability in cyclodextrin complexes is related to the hydrophobicity of the inner cyclodextrin cavity.

The aim of the present invention is to provide a composition for ophthalmological use in the form of an aqueous solution of a bispilocarpic acid diester, which provides for an increase in the total amount of drug delivered to the eye, for a prolonged duration thereof, while simultaneously reducing its peak concentration and associated side effects, such as eye irritation. By means of the composition the number of daily administration times may be reduced, which leads to improved patient compliance.

According to the invention it has now been discovered that by forming a complex between the bispilocarpic acid diesters and cyclodextrin, it is possible to regulate the uptake of drug into the cornea.

Based on the favourably symmetrical structure of the guest molecules with more than one hydrophobic part, complexes other than 1:1 are possible, thus reinforcing the advantageous effects of the cyclodextrins.

The object of the invention is thus a composition for the topical administration of bispilocarpic acid diester to the eye in the form of an aqueous solution, which is characterized in that it includes cyclodextrin.

The cyclodextrin molecules form complexes with some of the prodrug molecules in the composition, while some remain free in the solution.

Upon administration of a bispilocarpic acid diester eyedrop, neutralization of the solution in the precorneal area takes place. Neutralized bispilocarpic acid diester is absorbed more readily into the eye resulting in unwanted high peak concentration of bispilocarpic acid diester in the corneal epithelium, which leads to eye irritation. Cyclodextrin prevents the rapid uptake of neutral, free prodrug by complexing some of the neutral drug. When free prodrug is absorbed into the eye, the cyclodextrin-prodrug-complex liberates prodrug molecules according to the laws of equilibrium. By using suitable cyclodextrin concentrations, it is thus possible to reduce peak prodrug concentrations in the corneal epithelium, and thus reduce the degree of associated eye irritation.

According to a preferred embodiment, the cyclodextrin is included in an amount of 1 - 40 % (weight/volume).

As the cyclodextrin compound, any pharmaceutically acceptable cyclodextrin derivative, whether of α-, β- or γ-type, may be used. The cyclodextrin may also be substituted in one or more of the 2-, 3- and/or 6-positions. Typically they are cyclodextrin ethers, preferably lower alkyl or lower hydroxyalkyl, e.g. methyl, ethyl, hydroxyethyl, hydroxypropyl, e.g. 2-hydroxypropyl derivatives and esters such as acylates, sulfonates, sulfates and phosphates, or mixed derivatives. Increased water solubility and beneficial viscosity and mucoadhesive properties can also be gained by exploiting suitable branched cyclodextrins, such as their glucosyl and maltosyl derivatives, or linear covalently bonded oligomers and other linked or polymeric cyclodextrins, or their combinations. In general derivatives with hydroxy-substituted side chain have a better

solubility, viscosity and adhesion characteristics, where desired.

For economical reasons and availability the cyclodextrin is a β-cyclodextrin, preferably a β-cyclodextrin alkylated and/or hydroxyalkylated in the 2-,3- and/or 6-position.

Good results have been obtained with 2-hydroxypropyl-β-cyclodextrin (2-HP-β-cyclodextrin).

According to a further embodiment of the invention, the composition may, in addition, contain a viscosity enhancing agent and the viscosity is adjusted to the desired level with a substance suitable for the purpose. Typical examples are the cellulose derivatives, such as hydroxypropylmethylcellulose, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylalcohols, dextrans, polyacrylic acids, chitosans, hyaluronic acid etc. The amount of polymer to be added depends on the desired viscosity level, and on the polymer used, and can be easily determined by a person skilled in the art.

The viscosity enhancing agent is thus used in an amount to provide a suitable thickness to the composition, which usually means a viscosity of 1 - 25000 mPas. The viscosity is measured with a Brookfield viscosimeter (type LVDV-III) at a the temperature of 22 °C and a shear rate (D) of 1 s^{-1} for viscosities of 100 - 25000 mPas, and a shear rate of 60 s^{-1} for viscosities of 1 - 100 mPas.

The amount naturally varies according to the agent used. When using the first mentioned cellulose derivative (HPMC) an amount of 0.3 - 1 % gives a viscosity of appr. 10 - 150 mPas, a preferable range being 15 - 50 mPas.

The viscosity enhancing agent provides for a longer contact time of the composition with the eye surface, the total

amount of the drug absorbed thus being increased as well as providing for a prolonged action. The viscosity enhancing agent also slows down the neutralization rate of the acidic or slightly acidic composition on the eye surface, which in turn affects the uptake of prodrug, as the fat solubility of the BD's is all the more pronounced, the more neutral the solution is. The uptake of prodrug may thus be controlled to some extent also in this manner.

The compositions according to the invention may also include further adjuvants, for example preservatives, such as quaternary ammonium compounds, e.g. benzalkonium chloride, benzyl alcohol, mercury salts, thiomersal, chlorhexidine, chlorobutanol or the like.

According to the invention, the composition may in addition contain a buffer. As suitable buffering systems according to the invention may be mentioned phosphate buffers, borate buffers, acetate buffers and citrate buffers, or mixed buffers.

The buffers are usually used, depending on the desired pH and buffering capacity desired, in concentrations of 5 to 100 mM. The choice of amount and kind of buffer lies within the knowledge of the person skilled in the art.

By using a buffer, the above mentioned effect of slowing down the neutralization rate of the composition on the eye surface, and thus avoiding the initial undesired peak concentrations of pilocarpine, may be enforced. In combination with cyclodextrin, the buffer may regulate the equilibrium of complexed and free prodrug.

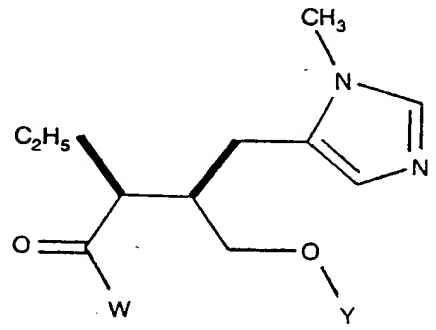
The pH of the composition is preferably 3 - 8, advantageously approximately 5 - 7.

The composition according to the invention is preferably

used in the form of an isotonic solution (corresponding to a 0.9 % NaCl-solution) and the tonicity may be varied by using substances conventionally used for this purpose, such as sodium chloride, potassium chloride, glycerol, mannitol, sorbitol, xylitol, sodium borate, sodium acetate and the like.

The bispilocarpic acid diesters are preferably those compounds which are disclosed in the WO-publications 92/-09583 and 93/24466, the contents of which are included here for reference.

Specifically the WO-publication 92/09583 broadly claims i.a. compounds of the general formula



(I)

wherein

A) Y is hydrogen or $-\overset{O}{\overset{\|}{C}}-R$, wherein R is hydrogen, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl, C_2-C_{18}-alkynyl, optionally substituted C_3-C_7-cycloalkyl or C_3-C_7-cycloalkenyl, optionally substituted aryl or aryl lower alkyl, and

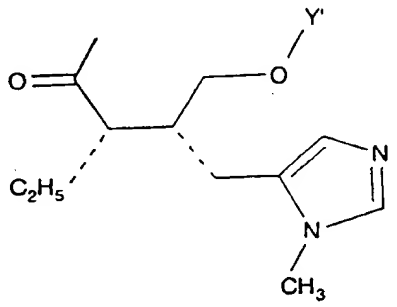
W is the group

$$-O-A-O-Z-Y'$$

wherein Y' has the meaning of hydrogen or the group $-\overset{O}{\overset{\|}{C}}-R'$, wherein R' has the meaning of R above, whereby R' can be the same as or different from R, A is optionally hydroxy or

protected-hydroxy substituted C_1-C_{18}-alkylene, C_2-C_{18}-alkenylene, C_2-C_{18}-alkynylene, which may be substituted by optionally substituted C_3-C_7-cycloalkyl, C_3-C_7-cycloalkenyl, aryl, or aryl lower alkyl, or A is optionally substituted C_3-C_7-cycloalkylene or C_3-C_7-cycloalkenylene or arylene, or A is the aforementioned alkylene, alkenylene, or alkynylene, which as a chain member contains the afore defined cycloalkylene, cycloalkenylene or arylene group, and

-Z-Y' is

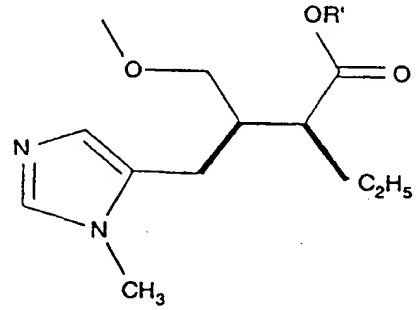


or

B) W is -OR, wherein R has the meaning given above, Y is

-C-B-C-Z'-OR', wherein R' has the meaning given above and B has the meaning given for A above, and

-Z'-OR' is



as well as the acid addition salts of the said compounds.

Preferred compounds are e.g. the diacyl bispilocarpates according to formula IA), wherein acyl is lower alkyl(1-4C)-, lower cycloalkyl(3-6C)-carbonyl or benzoyl, A is lower alkylene(2-6C), lower cycloalkylene(3-6C) or arylene, specifically O,O'-diacetyl-, O,O'-dipropionyl-, O,O'-

dibutyryl-, O,O'-valeryl- and O,O'-dicyclopropylcarbonyl (1,4-, 1,3-, 1,2-xylylene)- and -(1,2-ethylene)-, -(1,3-propylene)-, -(1,4-butylene)-, -(1,5-pentylene)- and -(1,6-hexylene) bispilocarpate, especially -(1,4-xylylene) bispilocarpate, the alkylene groups optionally being substituted with hydroxy or protected hydroxy, or with one or two methyl groups. - Of these may be mentioned those, wherein A is ethylene, or A is 1,3-propylene, which can be substituted in its 2-position with hydroxy, the group Y-O- wherein Y has the meaning given, or with one or two methyl groups.

A subgroup of the compounds of the formula IB) is formed by the compounds, wherein W is OR', wherein R' has the meaning of C_1-C_4-alkyl or C_3-C_6-cycloalkyl, and B is 1,2-ethylene, 1,3-propylene or 1,4-butylene.

Another preferred group of compounds of the formula IB) is comprised of e.g. the (dibenzyl) and (dilower alkyl) bispilocarpates, such as O,O'-glutaryl-, O,O'-disuccinyl-, O,O'-adipoyl (dibenzyl)- and -(dilower alkyl) bispilocarpate.

Specifically the following compounds may be mentioned:
O,O'-dipropionyl (1,4-xylylene) bispilocarpate
O,O'-dibutyryl (1,4-xylylene) bispilocarpate
O,O'-dicyclopropylcarbonyl (1,4-xylylene) bispilocarpate
O,O'-dipropionyl (1,6-hexylene) bispilocarpate
O,O'-dibutyryl (1,6-hexylene) bispilocarpate
O,O'-dicyclopropylcarbonyl (1,6-hexylene) bispilocarpate.

According to the invention it is possible to achieve sufficient drug absorption and prolonged duration of action with smaller amounts of drug as compared to pilocarpine, and thus the number of daily administration times may be reduced. The concentration of the BD's in the composition

according to the invention may vary, but is suitably from 0.05 - 4, preferably 0.5 - 2 weight %, calculated as the pilocarpine base. In connection with the latter limits of BD concentration, the concentration of cyclodextrin is preferably 5 - 20 % by weight.

The following Examples illustrate the invention, but are not intended to limit the same. The amount of active ingredient (in w/v) refers to the pilocarpine base.

Example 1

A composition according to the invention was made having the following ingredients:

O,O'-Dipropionyl (1,4-xylylene) bispilocarpate		24.4	mg
2-HP-β-cyclodextrin		50.0	mg
NaCl		4.0	mg
NaOH	ad pH	5.0	
Aq. ster.	ad	1.0	ml.

The concentration of active ingredient is 1.0 % and it contains 5% (w/v) of cyclodextrin. The pH of the solution is 5.

Example 2

A composition according to the invention was made having the following ingredients:

O,O'-Dipropionyl (1,4-xylylene) bispilocarpate		24.4	mg
2-HP-β-cyclodextrin		100.0	mg
NaCl		2.5	mg
NaOH	ad pH	5.0	
Aq. ster.	ad	1.0	ml.

The concentration of active ingredient is 1.0 % and that of cyclodextrin is 10 % (w/v). The pH of the solution is 5.

Example 3

A composition according to the invention was made having the following ingredients:

O,O'-Dipropionyl (1,4-xylylene) bispilocarpate		24.4	mg
2-HP-β-cyclodextrin		150.0	mg
NaCl		1.0	mg
NaOH	ad pH	5.0	
Aq. ster.	ad	1.0	ml.

The concentration of active ingredient is 1.0 % and that of cyclodextrin is 15 % (w/v). The pH of the solution is 5.

Example 4

A composition according to the invention was made having the following ingredients:

O,O'-Dipropionyl (1,4-xylylene) bispilocarpate		12.2	mg
2-HP-β-cyclodextrin		50.0	mg
HPMC		6.5	mg
NaCl		5.5	mg
NaOH	ad pH	5.0	
Aq. ster.	ad	1.0	ml.

The concentration of active ingredient is 0.5 % and that of cyclodextrin is 5 % (w/v). The viscosity is 50 cps and the pH of the solution is 5.

Example 5

A composition according to the invention was made having the following ingredients:

O,O'-Dibutyryl (1,4-xylylene) bispilocarpate		6.3	mg
2-HP-β-cyclodextrin		50.0	mg
NaCl		6.5	mg
NaOH	ad pH	5.0	
Aq. ster.	ad	1.0	ml.

The concentration of active ingredient is 0.25 % and that of the cyclodextrin 5 % (w/v). The pH of the solution 5.

Example 6

A composition according to the invention was made having the following ingredients:

O,O'-Dicyclopropylcarbonyl (1,4-xylylene) bispilocarpate		12.5 mg
2-HP-β-cyclodextrin		75.0 mg
NaCl		4.0 mg
NaOH	ad pH	5.0
Aq. ster.	ad	1.0 ml.

The concentration of active ingredient is 0.5 % and that of the cyclodextrin 7.5 % (w/v). The pH of the solution is 5.

Example 7

A composition according to the invention was made having the following ingredients:

O,O'-Dicyclopropylcarbonyl (1,4-xylylene) bispilocarpate		25.0 mg
2-HP-β-cyclodextrin		150.0 mg
NaCl		0.6 mg
NaOH	ad pH	5.0
Aq. ster.	ad	1.0 ml.

The concentration of active ingredient is 1.0 % and that of the cyclodextrin 15 % (w/v). The pH of the solution is 5.

Example 8

A composition according to the invention was made having the following ingredients:

O,O'-Dicyclopropylcarbonyl (1,6-hexylene) bispilocarpate		12.2 mg
2-HP-β-cyclodextrin		100.0 mg
NaCl		4.0 mg
NaOH	ad pH	5.0
Aq. ster.	ad	1.0 ml.

The concentration of active ingredient is 0.5 % and that of the cyclodextrin is 10 % (w/v). The pH of the solution is 5.

Example 9

A composition according to the invention was made having the following ingredients:

O,O'-Dicyclopropylcarbonyl (1,6-hexylene) bispilocarpate		24.5 mg
2-HP-β-cyclodextrin		200.0 mg
NaCl		1.0 mg
NaOH	ad pH	5.0
Aq. ster.	ad	1.0 ml.

The concentration of active ingredient is 1.0 % and that of the cyclodextrin is 20 % (w/v). The pH of the solution is 5.

The compositions according to the invention (compositions according to the Examples 1-9) were compared on the one hand to a commercial pilocarpine formulation (Oftan Pilocarpine 2%; reference composition 1) and on the other hand to compositions of the same prodrug in an aqueous solution without cyclodextrin (reference compositions 2-5) in the same tests and under the same conditions.

1. Miosis and degree of eye irritation caused by an aqueous cyclodextrin containing solution in rabbit

25 µl of each of the compositions to be tested were introduced in a rabbit eye, whereafter the degree of eye irritation caused by the composition was evaluated. The eye was photographed at regular intervals. The miosis caused by the tested compositions was determined from the negatives. With all compositions, at least 6 parallel tests were run. From the results was calculated:

a) AUC (area under curve; relates to the amount of drug absorbed)
b) Maximum miosis (maximum contraction of the pupil in percentages, compared to time 0)
c) Time to reach maximum miosis (t_{max})
d) Total time during which maximum miosis is > 3 %

The results are shown in Tables 1 and 2, and in Fig. 1A and 1B.

Table I

Composition	Conc. of solution (%)	$AUC_{0-360\ min}$ (% min) (x±S.E.)	Max. miosis (%) (x±S.E.)	t_{max} (min) (x±S.E.)	$t_{miosis>3\%}$ (min) (x±S.E.)	irritation[a] eye closed	eye half-open
Ref. comp. 1	2.0	1588±471	21±3	43±5	154±20	+	+++
Ref. comp. 2	0.5	1258±273	13±2	73±24	188±28	++	++++
Example 1	1.0	2189±414	13±1	126±15	267±36	+++	++++
Example 2	1.0	2318±396	13±1	103±24	276±32	+	+++
Example 3	1.0	3008±584	14±2	132±44	279±45	-	+
Example 4	0.5	3894±455	20±2	133±28	346±5	+++	++++

[a]Eye-irritation:
no irritation = -
< 0.5 min = +
0.5-1 min = ++
1 - 3 min = +++
> 3 min = ++++

Table II

Composition	Conc. of solution (%)	$AUC_{0-360\ min}$ (% min) (x±S.E.)	Max. miosis (%) (x±S.E.)	t_{max} (min) (x±S.E.)	$t_{miosis>3\%}$ (min) (x±S.E.)	irritation[a] eye closed	eye half-open
Ref. comp. 1	2.0	1588±471	21±3	43±5	154±20	+	+++
Ref. comp. 3	0.25	2484±508	15±2	73±8	240±35	++	+++
Example 5	0.25	1362±305	11±1	90±13	218±44	–	+
Ref. comp. 4	0.25	1734±431	10±2	65±18	235±31	+	++
Example 6	0.5	2081±478	12±1	50±20	288±29	–	++
Example 7	1.0	2817±641	14±2	108±24	272±35	++	+++
Ref. comp. 5	0.5	1871±298	9±1	68±13	259±31	+++	+++
Example 8	0.5	1223±254	8±1	90±32	203±43	–	++
Example 9	1.0	1674±508	10±2	85±30	225±49	++	+++

[a] Eye-irritation:
no irritation = –
< 0.5 min = +
0.5 – 1 min = ++
1 – 3 min = +++
> 3 min = ++++

The results show:

a) The compounds are absorbed from an aqueous cyclodextrin containing solution into the cornea and release pilocarpine in a controlled manner causing miosis.

b) With a composition containing 1 % prodrug and cyclodextrin (Example 3) a 1.9 times higher absorption of pilocarpine into the eye (AUC) is obtained than with commercial 2% pilocarpine (reference composition 1) and even 2.4 times better total absorption than with a 0.5 % prodrug alone (reference composition 2) with comparable or lesser degree of eye irritation.

The amount of prodrug absorbed from a cyclodextrin solution is dependent on the complexation constant of the prodrug with the cyclodextrin molecule. The complexation constant in turn is affected by the physico-chemical properties of prodrug and cyclodextrin. Also the concentration ratio of prodrug and cyclodextrin in the solution affects the fractions of complexed and free prodrug.

c) A composition containing 1 % prodrug in a cyclodextrin solution gives substantially longer miosis as compared to the reference composition 1 (Examples 2 and 3: 1.8 times longer) and also as compared to the reference composition 2 (Examples 2 and 3: 1.5 times longer).

d) Maximum miosis caused by the compositions according to the invention is lower than that of the reference composition 1, even though the total amount of drug absorbed is twice as big as that from the reference composition 1.

The lower maximum miosis shows that the compositions of the invention are able to reduce the peak concentration of pilocarpine, thus reducing the side effects in the eye.

e) Maximum miosis of the compositions of the invention is reached three times as late as compared to the reference composition 1. The maximum miosis is also reached later (1.5 times as late) from a composition containing cyclodextrin than when administering the prodrug from an aqueous solution without cyclodextrin (reference composition 2). This demonstrates the slower rate of prodrug absorption from a cyclodextrin complex.

f) By means of the cyclodextrin containing compositions according to the invention, especially see Example 3, it is possible to substantially reduce the degree of eye irritation caused by the prodrug in an aqueous solution, while simultaneously enabling increased drug absorption and prolongation of miosis.

g) When using a viscous cyclodextrin solution, the compounds are absorbed appr. 1.3 times better and provide for a 1.2 times longer lasting miosis than the corresponding prodrug molecule in a cyclodextrin solution without a viscosity enhancing agent (Table 1).

In Figure 1A, the change in pupil diameter (in %) is shown as a function of time for reference compositions 1 and 2, as well as for the composition according to Example 3.

In Figure 1B the duration of eye irritation is shown for the same compositions as in Figure 1A.

Claims

1. Composition for the topical administration of bispilocarpic acid diesters to the eye in the form of an aqueous solution, **characterized** in that it includes cyclodextrin.

2. Composition according to claim 1, **characterized** in that the amount of cyclodextrin is 1 - 40 % (weight/volume) of the total composition.

3. Composition according to claim 1 or 2, **characterized** in that the cyclodextrin is selected from the group consisting of unsubstituted and lower alkyl and lower hydroxyalkyl substituted β-cyclodextrins.

4. Composition according to any of the previous claims, **characterized** in that in addition includes a viscosity enhancing agent.

5. Composition according to claim 4, **characterized** in that the viscosity enhancing agent is selected from the group consisting of hydroxypropylmethylcellulose, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylalcohols, dextrans, polyacrylic acids, chitosans, and hyaluronic acid.

6. Composition according to claim 5, **characterized** in that the viscosity enhancing agent is hydroxypropylmethylcellulose (HPMC).

7. Composition according to claim 4, **characterized** in that the viscosity enhancing agent is included in an amount to give a viscosity in the range of 1 - 250000 mPas.

8. Composition according to claim 1, **characterized** in that it is an isotonic solution.

9. Composition according to claim 1, **characterized** in that it includes a buffer.

10. Composition according to claim 9, **characterized** in that the buffer is selected from the group consisting of phosphate buffers, borate buffers, acetate buffers and citrate buffers, or mixed buffers.

11. Composition according to claim 10, **characterized** in that it is buffered with a citrate buffer.

12. Composition according to any preceeding claim, **characterized** in that its pH is 3 - 8, preferably 5 - 7.

13. Composition according to any one of the preceeding claims, **characterized** in that the bispilocarpic acid diester is a O,O'-diacyl (1,4-xylylene) bispilocarpate, wherein acyl is selected from the group consisting of lower alkyl- or lower cycloalkylcarbonyl.

14. Composition according to claim 1, **characterized** in that the bispilocarpic acid diester is O,O'-dipropionyl, O,O'-dibutyryl or O,O'-dicyclopropylcarbonyl (1,4-xylylene) or (1,6-hexylene) bispilocarpate.

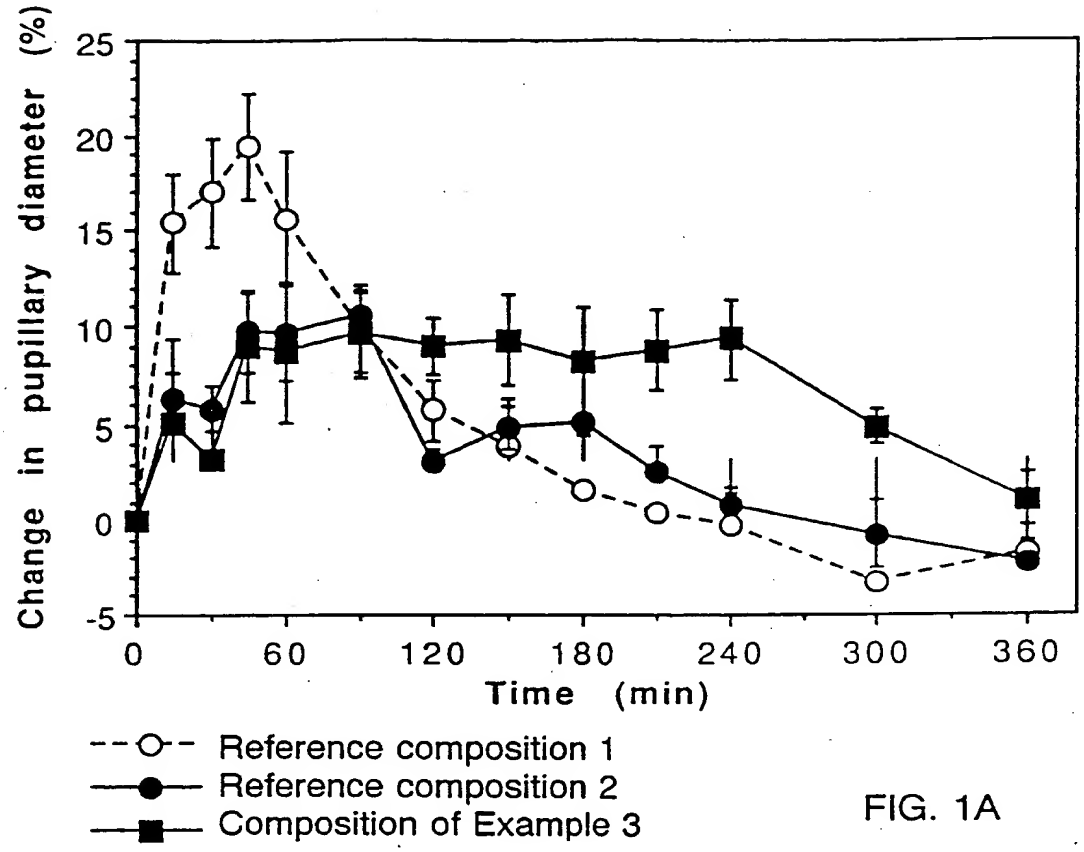

Change in pupillary diameter (%)
25
20
15
10
5
0
-5
0
60
120
180
240
300
360
Time (min)
Reference composition 1
Reference composition 2
Composition of Example 3

FIG. 1A

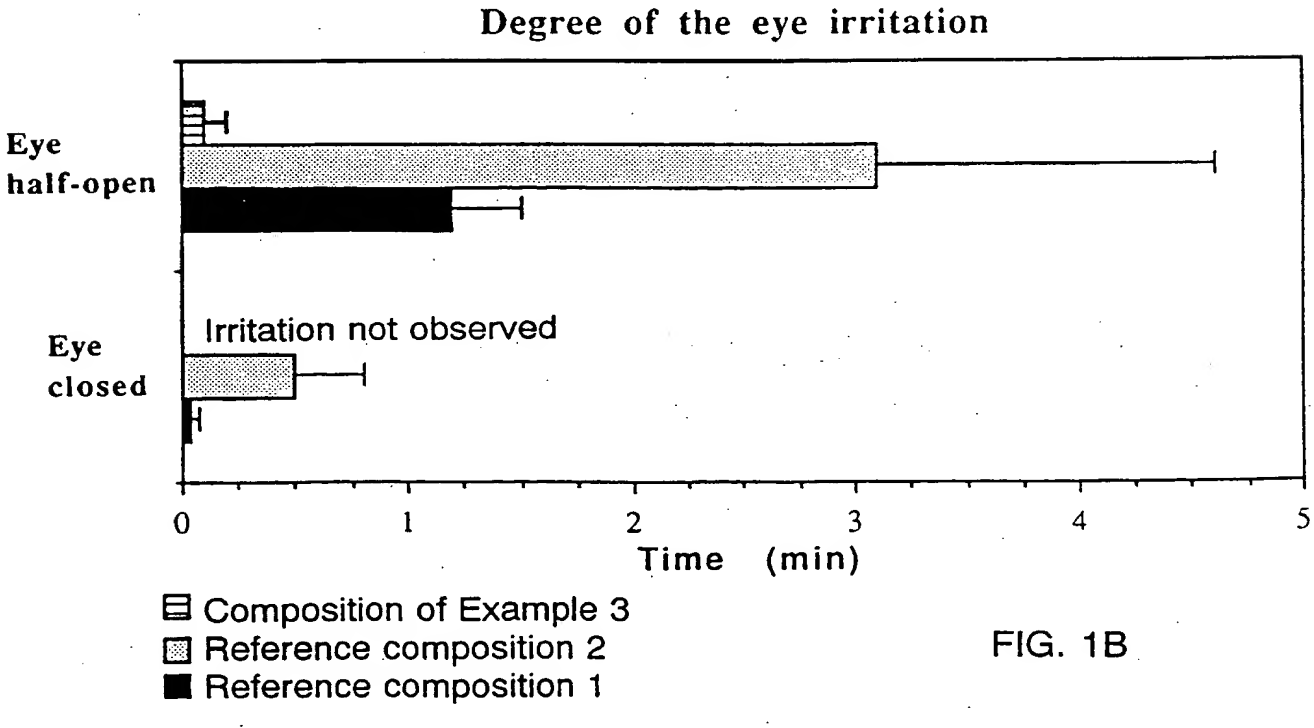

Degree of the eye irritation
Eye half-open
Eye closed
Irritation not observed
0
1
2
3
4
5
Time (min)
Composition of Example 3
Reference composition 2
Reference composition 1

FIG. 1B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00270

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/415, A61K 9/06, A61K 47/36, A61K 47/40
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0082921 (KAKENYAKU KAKAO CO., LTD.), 6 July 1983 (06.07.83), page 7, line 38 - page 8, line 35, the claims --	1-14
A	EP, A1, 0472327 (SENJU PHARMACEUTICAL CO., LTD.), 26 February 1992 (26.02.92), page 3, line 37 - line 52, the claims --	1-14
A	WO, A1, 9209583 (HUHTAMÄKI OY), 11 June 1992 (11.06.92), page 15, line 13 - line 22; page 16, line 14 - line 30; page 11, line 10 - line 12, claims 1, 3, 6 --	1-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 Sept 1994	11 -10- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00270

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	International Journal of Pharmaceutics, Volume 75, 1991, Tomi Järvinen et al, "0,0'-(1,4-Xylylene) bispilocarpic acid esters as new potential double prodrugs of pilocarpine for improved ocular delivery. II. Physicochemical properties, stability, solubility and enzymatic hydrolysis", page 259 - page 269, see page 262, 264, 265, 268	1-14

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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/08/94

International application No.
PCT/FI 94/00270

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0082921	06/07/83	AT-B- 385201	10/03/88
		AU-B- 549419	23/01/86
		AU-A- 9175282	30/06/83
		CA-A- 1182751	19/02/85
		CH-A,B- 652598	29/11/85
		JP-A- 58126810	28/07/83
		US-A- 4474811	02/10/84
EP-A1- 0472327	26/02/92	AU-B- 633754	04/02/93
		AU-A- 8170891	20/02/92
		CA-A- 2048942	14/02/92
		CN-A- 1059725	25/03/92
		JP-A- 5213757	24/08/93
WO-A1- 9209583	11/06/92	AU-A- 8939891	25/06/92
		CA-A- 2096444	31/05/92
		EP-A- 0559700	15/09/93
		JP-T- 6504270	19/05/94
		NZ-A- 240781	23/12/93